## REMARKS

The Official Action dated March 20, 2001 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, the specification is replaced with a substitute specification in which various changes for matters of form have been made in accordance with suggestions from the Examiner. Non-elected claims 22-41 have been cancelled and claims 1, 4, 6, 9 and 10 have been amended. Claim 1 is amended to more clearly recite a cytokine receptor protein and to include limitations from claim 3, claim 4 is amended to depend from and correspond with claim 1, and claim 6 is amended to clarify that the receptor is hGHR. Claims 9 and 10 are amended to clarify that the native molecule is hGHR. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, the Examiner made the restriction requirement under 35 U.S.C. §121 final. Accordingly, non-elected claims 22-41 have been cancelled from the application. It is believed that this represents a complete response to the restriction requirement.

The Examiner noted that the present application was filed as a 371 application of PCT/SE98/00277 filed September 17, 1998. The substitute specification submitted herewith includes a statement reciting this priority, as suggested by the Examiner.

The Examiner questioned the signature of Michael Sundström on the Declaration and Power of Attorney filed previously in this application. The undersigned has forwarded a statement to Mr. Sundström to confirm that the signature on the Declaration and Power of Attorney is his actual full name, and the executed statement will be forwarded to the Examiner once it is received by the undersigned.

The Notice of Draftsperson's Patent Drawing Review accompanying the Official Action objected to the Figures as comprising poor quality half-tone photographs. Substitute drawings are submitted herewith, and review and approval of the substitute drawings is requested.

In the specification, the Examiner requested that an Abstract on a separate sheet be required, that the list of references cited be incorporated into the text of the specification, that various grammatical errors throughout the specification be corrected and that Example 1 be rewritten. The substitute specification submitted herewith includes an Abstract on a separate sheet, incorporates the cited references into the text of the specification and clarifies the various sections and Example noted by the Examiner. It is therefore believed that the substitute specification overcomes the Examiner's objections, and reconsideration is respectfully requested.

Claims 1-9 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention commensurate in scope with the claims. Specifically, while the Examiner acknowledged that the specification is enabling for the modified human growth hormone receptor (hGHR) consisting of residues 32-237 of the native molecule of hGHR and capable of being crystallized without being complexed to a ligand molecule, the Examiner asserted that the present specification confirms that crystallization of cytokine receptor proteins is very unpredictable and the specification provides no guidance on how to make any modified extracellular domain of a cytokine receptor protein except for hGHR 32-237.

However, Applicants submit that the present claims are enabled in accordance with the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

According to claim 1, the invention is directed to a cytokine receptor protein modified in the extracellular domain, wherein at least one molecule segment which contributes to a disordered structure is deleted, the modified protein being capable of being crystallized without being complexed to a ligand molecule. Modifications to the cytokine receptor protein's extracellular domain are, in fact, what render crystallization of these modified proteins more predictable than the prior art. At page 3, lines 4-8, the original specification teaches that the inventive modifications are easily accomplished by techniques well known in the art. In addition, Applicants describe how to determine, based on the readily ascertainable structure of the extracellular domain, which segment(s) of the extracellular domain portion of the molecule contribute to disorder in the crystalline state, and, therefore, which residues should be deleted in accordance with the invention. The Examiner's attention is directed to page 2, lines 2-5 and page 4, lines 14-29 of the original specification. Once modified in this manner to the inventive form, crystallization of the unliganded cytokine receptor protein is rendered predictable in comparison to the prior art. In addition, the disclosure explicitly states on page 2, lines 6-8, that the object of the invention is to "provide modified extracellular domains of cytokine receptors . . . which are capable of being crystallized with conventional methods". Hence, enablement of the crystallization exists once the modified receptor protein if derived in accordance with the teachings of the specification.

As a matter of Patent Office practice, a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support, *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971) (emphasis by court). In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of

any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement, *Id.*, at 370 (emphasis by court). The present specification disclosure contains a teaching of the manner and process of making the modified cytokine receptor protein in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented and therefore must be taken as in compliance with the enabling requirement of 35 U.S.C. §112, first paragraph. It is therefore submitted that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-10 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. However, Applicants submit that the present claims are definite in accordance with the requirements of 35 U.S.C. § 112, second paragraph. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More specifically, in claims 1 and 6, the Examiner asserted it was not clear whether the invention was directed to merely the modified extracellular domain of the receptor protein or the entire receptor where the extracellular domain is modified. Claim 1 clearly recites a modified cytokine receptor protein, while claim 6 recites the receptor as hGHR. It is therefore submitted that claims 1 and 6 are definite and that the rejection has been overcome.

Claim 3 was asserted to be indefinite for reciting "molecular segment which contributes to a disordered structure." Applicants note that this limitation is now in claim 1 and submit that the specification provides reasonable guidance for determining which molecular segment contributes to the disordered crystalline structure for a given cytokine receptor protein. The original specification discloses at page 2, lines 4-5 that these regions most likely contain domains and/or loop regions that are flexibly connected which contributes to a disordered state which obstructs crystallization. At page 4, lines 14-29 of the original specification, Applicants disclose that the skilled artisan can use standard crystallographic techniques to determine the receptor-ligand three dimensional structure. Then, using the

detailed guidance provided in the original specification on pages 6 and 7, combined with the techniques and observations found in Sundström, et al. (1996) p. 32197-32203 (cited a Sundstrom et al, in press, in the original specification), the skilled artisan can determine which molecular segments to delete in order to achieve the inventive modified receptor. "Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made," *In re Moore*, 169 U.S.P.Q. 236 (CCPA 1971). When claim 1 is viewed in light of these considerations, claim 1 is definite to one skilled in the art in accordance with 35 U.S.C. §112, second paragraph.

Claims 4 and 5 were asserted as indefinite on the basis that the "extent of truncation" is not defined. Claim 4 recites that the modified protein is truncated to delete the molecule segment which contributes to a disordered structure. Applicants therefore submit that the extent of truncation is dependent upon the length of the molecular region determined to contribute to the disordered crystalline state. Claims 4 and 5 depend from claim 1, which states that this disordering segment "is deleted." Applicants note that "truncation" is a term of art for deleting amino acid residues from one end of the molecule, as opposed to excision of a segment from an internal region of a molecule. Since the means for determining which molecular segment contributes to such disorder is revealed in the specification and prior art, the length of the molecular segment, and, therefore, the "extent of truncation" is determinable and definite to one of ordinary skill in the art for a given cytokine protein receptor. Applicants therefore submit that claims 4 and 5 are definite to one of ordinary skill in the art.

Claim 6 was asserted to be unclear on the basis that the recitation "being human growth hormone receptor (hGHR)" yields multiple interpretations as to the identity of the starting product. Following the Examiner's suggestion, claim 6 recites that the receptor is

human growth hormone receptor (hGHR), making it clear that the starting material is hGHR. Hence, Applicants submit that claim 6 is definite to one of ordinary skill in the art.

Claims 7 and 8 were asserted to be indefinite on the basis that it was not clear in what consequential order amino acid residues are removed from the N- or C- terminal end of the molecule. Applicant submits that there is no suggestion in the claims, disclosure or prior art that there is a consequential order for removal of the amino acid residues. Proteolytic degradation is accomplished by any of several widely known techniques referenced in the specification and the order of removal in achieving the desired extent of truncation is not critical to making the inventive modified receptor protein. It is therefore submitted that claims 7 and 8 are definite to one of ordinary skill in the art.

Claims 9 and 10 were asserted to be indefinite on the basis that it was not clear to what "the native molecule" referred. The claims now recite "the native hGHR molecule." Hence, it is submitted that claims 9 and 10 are definite to one of ordinary skill in the art.

It is therefore submitted that claims 1 - 10 are definite and that the rejection under 35 U.S.C. § 112, second paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 1 and 2 were rejected under 35 U.S.C. § 102(b) as being anticipated by Muller et al, *J. Mol. Biol.*, 256:144-159 (1996). The Examiner stated that Muller et al. teach crystals of the extracellular domain of human tissue factor, hTF, a class II cytokine receptor that is an integral membrane glycoprotein consisting of 262 residues, and the Examiner asserted that the Muller et al crystals were free of ligands, had conformational modifications, and formed homodimers.

However, as set forth in detail below, Applicants submit that the cytokine receptor protein of claims 1 and 2 is not anticipated by Muller et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Claims 1 and 2 are directed to a cytokine receptor protein that is modified in the extracellular domain, wherein at least one molecule segment contributing to a disordered state is deleted. On the other hand, Muller et al disclose conformational modifications which are based on manipulations of the molecular environment. These manipulations engender conformational changes in the macromolecular protein structure. Applicant finds no suggestion or teaching in Muller et al of any deletion of a molecule segment from the extracellular domain.

Anticipation under 35 U.S.C. § 102 requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). Muller et al neither teach nor suggest a cytokine receptor protein modified in the extracellular domain as recited in claim 1. Thus, Muller et al do not disclose each element of claims 1 and 2 and therefore do not anticipate these claims under 35 U.S.C. §102.

It is therefore submitted that the cytokine receptor protein defined by claims 1 and 2 are not anticipated by Muller et al, and that the rejection under 35 U.S.C. § 102 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§ 102 and 112, first and second paragraphs, and places the present application in condition for allowance. Reconsideration and early allowance are respectfully requested.

Respectfully submitted,

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## VERSION WITH MARKINGS SHOWING CHANGES MADE

Claims 1, 4, 6, 9 and 10 are amended as follows:

1. (Amended) A cytokine receptor protein modified in the extracellular domain [of a cytokine receptor protein], wherein at least one molecule segment which contributes to a disordered structure is deleted, the modified protein being capable of being crystallized without being complexed to a ligand molecule.

4. (Amended) A modified protein according to claim 1 [3] truncated in at least one terminal end to delete the molecule segment which contributes to a disordered structure.

6. (Amended) A modified protein according to claim 5 [being] wherein the receptor is human growth hormone receptor (hGHR).

9. (Twice Amended) A modified human growth hormone receptor (hGHR) according to claim 6 consisting of residues 32-237, 32-234 or 34-233 of the native hGHR molecule.

10. (Twice Amended) A modified human growth hormone receptor (hGHR) according to claim 9 consisting of residues 32-237 of the native hGHR molecule.